REMARKS

Rejection of Claims 1-3 And 6 Under 35 USC §112, 1st Paragraph

Claims 1-3 and 6 stand rejected under 35 U.S.C. §112, first paragraph, for failing to comply with written description requirement. Claims 1-3 and 6 are also rejected under 35 U.S.C. §112, first paragraph, for introducing new matter. Applicants respectfully traverse this rejection.

More specifically, the Examiner contends that reciting "immunological tolerance" in claim 1 introduces new matter which is not supported by the specification as filed. Applicant submit that claim 1 has been amended to delete the phrase "immunological tolerance".

The Examiner further rejected claims 1-3 and 6 under 35 U.S.C. §112, first paragraph, for lack of enablement to the extent that the claimed methods are not described in the disclosure. Applicant submits that since claim 1 has been amended to delete the new matter, this rejection is moot. Accordingly, Applicant respectfully requests that the rejection of claims 1-3 and 6 under 35 U.S.C. §112, first paragraph, be withdrawn.

Rejection of Claims 1-3, 6 And 24-29 Under 35 USC §112, 1st Paragraph

Claims 1-3, 6 and 24-29 are rejected under 35 U.S.C. §112, first paragraph, for lack of enablement. The Examiner contends that heat-labile enterotoxins are mucosal adjuvants and the specification fails to teach that a mucosal adjuvant could be used in a non-mucosal route (such as intramuscular route) to achieve the same effects as those obtained via mucosal delivery. The rejection is respectfully traversed.

Claim 6 has been amended to recite delivery of heat-labile enterotoxins via a mucosal route such as oral, intranasal, intrarectal, or intravaginal administration. Applicant submits that the mucosal routes recited in amended claim 6 are all well recognized in the art, and one of ordinary skill in the art would be able to administer without undue experimentations a mucosal adjuvant via one of the recited mucosal routes. Furthermore, Applicant submits that one of ordinary skill in the art would reasonably expect similar effects upon administering a mucosal adjuvant in different mucosal tissues. Hence, one of ordinary skill in the art would reasonably expect that oral, intrarectal or intravaginal administration of heat-labile enterotoxins would

achieve the same effects as those obtained via intranasal delivery as described in the specification. Accordingly, Applicant submits that the scope of claim 6 is commensurate with the scope of enablement provided.

The Examiner also contends that the specification fails to support the claims on using the recited recombinant heat-labile enterotoxins to increase Th1 response and cell-mediated immunity. This rejection is respectfully traversed.

Applicant submits that the specification has provided ample evidence on differential induction of Th1/Th2 responses by heat-labile enterotoxins. Figures 6C, 6D, and 6E show that exposure of stimulated T cells to LTIIa or LTIIb permits the release of IL-2, TNF-alpha, and IL-12 by T cells, whereas exposure to CT suppresses the release of these cytokines. Conversely, Figures 6A and 6B show that exposure of stimulated T cells to LTIIa or LTIIb slightly suppresses the release of IL-4 and IL-10 as compared to exposure to CT. It is well-known in the art that IL-4 and IL-10 are associated with Th2 activity whereas IL-2, TNF-alpha and IL-12 are associated with Th1 activity. Thus, these figures show evidence of differential Th1/Th2 stimulation by CT vs LTIIa or LTIIb: i.e. CT promotes Th2, whereas LTIIa and LTIIb promote Th1.

Figure 7 reveals that T cells respond differently to CT and LTIIa or LTIIb: CT suppresses the expression of CD40 ligand on T cells, LTIIa and LTIIb do not. Thus when these T cells are co-cultured with antigen presenting cells which express CD40 (monocytes in Figures 8A and C, monocyte-derived dendritic cells in Figures 8B and D), IL-12 production (Figures 8A and B) or TNF-alpha production (Figures 8C and D) are consequently suppressed by pretreatment of the T cells with CT but not with LTIIa or LTIIb. These T cell-antigen presenting cell costimulations were dependent upon CD40-CD40 ligand interactions because anti-CD40 ligand antibody inhibited the interactions. However, LTIIa- or LTIIb-induced TNF-alpha release was only partially inhibited by anti-CD40 ligand antibody, whereas CT-induced TNF-alpha release was almost completely inhibited (Figs 8C and D). This reveals a differential Th1/Th2 effect of CT and LTIIa or LTIIb.

The Examiner contends that the specification fails to disclose any evidence that is contrary to what was known in the art as taught by Rappuoli et al. that "polarization in the T cell response is much less pronounced when LT is used as a mucosal adjuvant, with both Th1 and Th2 cells being activated." Applicant respectfully disagrees. Applicant submits that Figures 6-8 have provided clear

and convincing evidence that is contrary to what was taught by Rappuoli et al.

The Examiner also contends that one cannot predictably determine the immunoadjuvant effect of LTIIaA2/B using the results of LT-II whole molecule because Rappuoli et al. teach that "recent studies suggest that LT mutants with one single amino acid substitution in the A subunit have different behaviors in the activation of the $CD4^+$ cell subpopulation." Applicant respectfully disagrees. Applicant submits that the teaching of Rappuoli et al. is not relevant to the present invention because Rappuoli et al. only teach single amino acid substitution (LTK63 or LTR72) in the A1 subunit of heat-labile enterotoxin, whereas the present invention is drawn to an immunogen comprising the A2 and B subunits of a type II heat-labile enterotoxin. Rappuoli et al. do not teach or suggest any unusual or unpredictable activity for a LT mutant comprising the A2 and B subunits as claimed herein.

Applicant further submits that in view of the data (Figures 6-8) showing preferential induction of Th1 responses by type II heat-labile enterotoxin and the well-known fact that cell-mediated immune responses are driven by Th1 type T cell help, one of ordinary skill in the art would reasonably infer that an

immunogen comprising the A2 and B subunits of a type II heat-labile enterotoxin could enhance or promote cell-mediated immune response. Hence, Applicant submits that the scope of the claimed methods is commensurate with the enablement provided, and no undue experimentation is required to determine the parameters of using recombinant heat-labile enterotoxins to increase Th1 response and cell-mediated immunity. Accordingly, Applicant respectfully requests that the rejection of claims 1-3, 6 and 24-29 under 35 U.S.C. §112, first paragraph, be withdrawn.

Rejection of Claims 1, 2, 25 and 28 Under 35 USC §112, 2nd Paragraph

Claim 1 stands rejected for reciting "the antigen sequence" without sufficient antecedent basis. Applicant submits that claim 1 has been amended to delete the phrase "the antigen sequence".

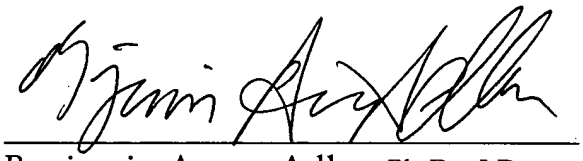
Claims 2, 25 and 28 stands rejected for reciting "said antigen of interest" without sufficient antecedent basis. Applicant submits that claims 1, 24 and 27 have been amended to recite "an antigen of interest" to provide antecedent basis for the limitation in claims 2, 25 and 28. Accordingly, Applicant respectfully requests

that the rejection of claims 1, 2, 25 and 28 under 35 U.S.C. §112, second paragraph, be withdrawn.

This is intended to be a complete response to the Office Action mailed February 25, 2004. If any issues remain outstanding, the Examiner is respectfully requested to telephone the undersigned attorney of record for immediate resolution.

Respectfully submitted,

Date: June 4, 2004



Benjamin Aaron Adler, Ph.D., J.D.
Registration No. 35,423
Counsel for Applicant

ADLER & ASSOCIATES
8011 Candle Lane
Houston, Texas 77071
(713) 270-5391 (tel.)
(713) 270-5361 (facs.)
badler1@houston.rr.com